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(54) **17-Spirofuran-3'-ylidene steroids.**

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EP-A- 0 116 974
EP-A- 0 289 073
EP-A- 0 321 010
WO-A-87/05908

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Description

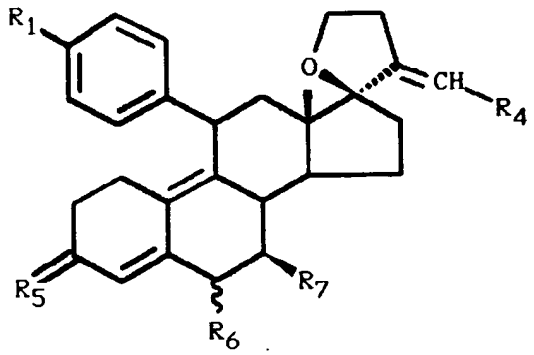
The invention relates to novel 17-spirofuran-3'-ylidene steroids, to methods of preparation thereof, a pharmaceutical composition containing the same, and a use of these steroids for the manufacture of a medicament having antiprogestin activity.

Antiprogestins, i.e. compounds which show affinity for the progesterone receptor, are known. One of the best known compounds in this respect is RU 486, which is disclosed in European patent 0,057,115.

In the PCT patent application WO-A-87/05908 antiprogestins are disclosed, which also display a marked antiglucocorticoid activity. Furthermore, antiprogestins are known from the European patent applications EP-A-321,010 and EP-A-289,073.

It has now been found that steroids having a 17-spirofuran-3'-ylidene ring show surprisingly strong affinity to the progesterone receptor, and, moreover, have at the same time decreased affinity to the glucocorticoid receptor. Further, the novel compounds have virtually no affinity to the mineralocorticoid receptor. The present steroids, therefore, show an improved selectivity and are more suitable for therapeutic use.

The 17-spirofuran-3'-ylidene steroids of the invention have a formula



I

wherein

R_1 is NR_2R_3, lower acyl, O-lower alkyl or S-lower alkyl;

R_2 and R_3 are independently selected from hydrogen and lower alkyl;

R_4 is hydrogen or lower alkyl;

R_5 is O, (H,H);

R_6 and R_7 are both hydrogen, or one is hydrogen and the other lower alkyl; and

the twitched line represents an α or β bond.

Preferred steroids according to the invention have formula I, wherein

R_1 is $N(CH_3)_2$, acetyl, or S-lower alkyl;

R_4 is hydrogen or methyl;

R_5 is O;

R_6 and R_7 are both hydrogen, or one is hydrogen and the other methyl.

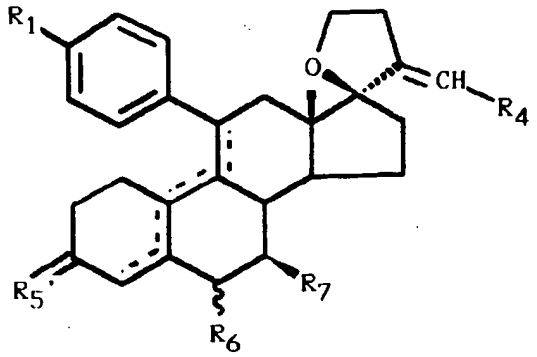
Most preferred is the 17-spirofuran-3'-ylidene steroid, wherein R_1 is acetyl, R_4 is hydrogen, R_5 is O, and R_6 and R_7 are both hydrogen.

The term lower alkyl means a branched or unbranched alkyl group having 1-6 carbon atoms, such as methyl, ethyl, propyl, isopropyl, butyl, *tert*-butyl, pentyl, hexyl and the like. Preferred alkyl groups have 1-4 carbon atoms, and most preferred is the methyl group.

The term lower acyl means an acyl group derived from an aliphatic carboxylic acid having 2-6 carbon atoms. Acetyl is the preferred acyl group.

When R_4 is an alkyl group Z- and E-isomers are possible. Both isomeric forms are considered to belong to this invention.

The 17-spirofuran-3'-ylidene steroids of this invention can be prepared in various ways. A convenient method is the cleavage of a protective group of a corresponding steroid in which the 3-keto is protected, which steroid has the formula



II

wherein

R_1 is NR_2R_3, lower acyl, O-lower alkyl, or S-lower alkyl;

R_2 and R_3 are independently selected from hydrogen and lower alkyl;

R_4 is hydrogen or lower alkyl;

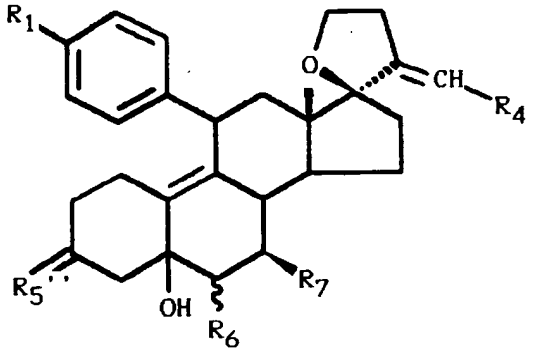
R_5' is a protected O;

R_6 and R_7 are both hydrogen, or one is hydrogen and the other lower alkyl; the dotted line represents two conjugated bonds, and

the twitched line represents an α or β bond.

Suitable protective groups are known in the art, for instance, from T.W. Green: Protective Groups in Organic Synthesis (Wiley, NY, 1981), which is included by reference. Particularly suitable are acetals for the protection of keto groups, for example 1,2-ethylene ketal. In this respect, also a dithioketal should be mentioned, which easily can be converted into a keto group by treatment with silver nitrate.

Another suitable method is the dehydration of a compound having formula

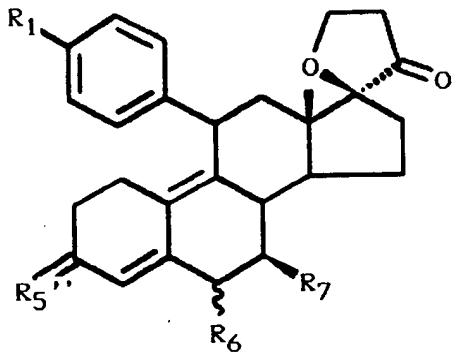


III

wherein

R_5" is protected O, (H,H), and R_1-R_4, R_6-R_7, and the twitched line have the previously given meanings. The protective groups, If present, are simultaneously cleaved or cleaved after the dehydration step. Dehydration is normally performed under acidic conditions, but also catalytic dehydration (for example using aluminum oxide), and indirect dehydration by converting the 5-hydroxy group into a suitable leaving group, which is removed together with an adjacent hydrogen atom, are possible. An example of the latter method is the conversion of the 5-hydroxy group into a halogen like iodide, followed by dehydrohalogenation under alkaline conditions.

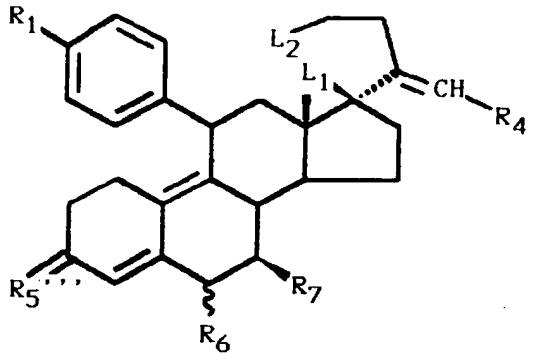
Yet another method is a Wittig, Wittig-like, or Peterson reaction using a compound having the formula



IV

wherein R_5'' is protected O, (H,H), and R_1-R_3, R_6-R_7, and the twitched line have the previously given meanings, and a R_4-CH_2-Wittig, R_4-CH_2-Wittig-like, or R_4-CH_2-Peterson reagent, wherein R_4 has the previously given meaning. This reaction is followed by deprotection of an optionally present protective group into the 17-spirofuran-3'-ylidene steroid of this invention. Suitable Wittig or Wittig-like reagents are triphenylphosphoranes such as R_4-CH_2-P(Hal)Ph_3, and the like, and suitable Peterson reagents are, for example, trimethylsilane reagents like R_4-CH(MgHal)Si$(CH_3)_3$, wherein Hal denotes a halogen like chlorine or bromine.

Alternatively, the 17-spirofuran-3'-ylidene steroids of this invention can also be prepared by ring closure to the 17-spirofuran-3'-ylidene ring. In this method a compound having the formula



V

wherein R_5''' is R_5 or protected O, (H,H), and R_1-R_7, and the twitched line have the previously given meanings, and one of L_1 and L_2 is OH and the other is a leaving group, is converted into a 17-spirofuran-3'-ylidene steroid, which after deprotection of an optionally present protective group affords the desired 17-spirofuran-3'-ylidene steroid. Leaving groups are known in the art. Suitable leaving groups are, for instance, hydroxy, halogen (particularly chlorine and bromine), and sulfonates such as *para*-toluene sulfonate and mesylate groups.

It is possible to convert the products obtained by one of the previously mentioned procedures into another product according to the invention. Using generally known methods it is, for instance, possible to convert steroids wherein R_2 and/or R_3 is hydrogen, for example, by a Leuckart-Wallach reaction, to afford steroids wherein R_2 and/or R_3 is alkyl.

The compounds of the invention may be administered enterally or parenterally, and for humans preferably in a daily dosage of 0,001-10 mg per kg body weight. Mixed with pharmaceutically suitable auxiliaries, e.g. as described in the standard reference, Gennaro et al., Remington's Pharmaceutical Sciences, (18th ed., Mack Publishing Company, 1990, see especially Part 8: Pharmaceutical Preparations and Their Manufacture) the compounds may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. a nasal spray. For making dosage units, e.g. tablets, the use of conventional additives such as fillers, colorants, polymeric hinders and the like is contemplated. In general any pharmaceutically

acceptable additive which does not interfere with the function of the active compounds can be used. Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof, used in suitable amounts.

The invention is further illustrated by the following examples.

EXAMPLE 1

(11β, 17α)-17,23-epoxy-11-[(4-dimethylamino)phenyl]-19,24-dinorchola-4,9,20-trien-3-one

a. To a solution of 25.6 g of (17β)-3-methoxyspiro-[estra-1,3,5(10)-triene-17,2'(3'H)-furan]-3'-one (see D. Gange and Ph. Magnus, J. Am. Chem. Soc., 100 (1978), 7746-7747) in 200 ml of ethanol and 200 ml of toluene were added 2.85 g of sodium borohydride, and the mixture was stirred at room temperature for 16 hours. Acetic acid was added until pH 7, followed by addition of water, and the mixture was extracted with toluene. Removal of the solvent under reduced pressure afforded the crude alcohol, which was crystallized from methanol to yield 24 g of (17β,3'S)-4',5'-dihydro-3-methoxyspiro[estra-1,3,5(10)-triene-17,2'(3'H)-furan]-3'-ol, m.p. 130 °C

b.

(i) A solution of 9 g of (17β,3'S)-4',5'-dihydro-3-methoxyspiro[estra-1,3,5(10)-triene-17,2'(3'H)-furan]-3'-ol in 150 ml of tetrahydrofuran was added to a solution of 4 g of lithium in 450 ml of liquid ammonia at -33 °C. After stirring for 3 hours at this temperature 60 ml of ethanol were added and the ammonia was allowed to evaporate. The residue was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure, affording after trituration with diisopropyl ether 8.9 g of (17β,3'S)-4',5'-dihydro-3-methoxyspiro[estra-2,5(10)-diene-17,2'(3'H)-furan]-3'-ol.

(ii) 8.9 g of the above-mentioned diene were dissolved in 65 ml of methanol and 65 ml of tetrahydrofuran. At 5 °C a solution of 4.6 g of oxalic acid in 45 ml of water and 22 ml of methanol was added. After stirring for 6 hours at ambient temperature the mixture was poured into an ice-cold 1% sodium hydrogen carbonate solution and extracted with ethyl acetate. The organic layer was washed with brine, dried over magnesium sulfate and concentrated under reduced pressure to give 8.5 g of the crude (17β,3'S)-4',5'-dihydro-3'-hydroxy-spiro[estr-5(10)-ene-17,2'(3'H)-furan]-3-one.

(iii) 8.5 g of this ketone were dissolved in 90 ml of pyridine. To this solution were added portionwise 10 g of phenyltrimethylammonium tribromide during 15 min at 0 °C. After stirring for 3 hours at room temperature the mixture was poured into 800 ml of ice-water and the product was extracted with ethyl acetate. The organic layer was washed with 2M hydrochloric acid, brine and dried over magnesium sulfate. The residue was chromatographed after evaporation of the solvent to yield 4.7 g of (17β,3'S)-4',5'-dihydro-3'-hydroxyspiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one, m.p. 180 °C.

c.

(i) A mixture of 4.1 g of (17β,3'S)-4',5'-dihydro-3'-hydroxyspiro[estra-4,9-diene-17,2' (3'H)-furan]-3-one, 30 ml of dichloromethane, 30 ml of ethylene glycol, 10 ml of triethyl orthoformate, and 200 mg of *para*-toluenesulphonic acid was stirred for 2 hours at room temperature. The reaction was stopped by the addition of water and sodium hydrogen carbonate, the layers were separated and the organic layer was washed with water. After drying over magnesium sulfate and concentration under reduced pressure 5.1 g of the crude (17β,3'S)-4',5'-dihydro-3'-hydroxyspiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one 3-cyclic 1,2-ethanediyl acetal were obtained, which was used in the next step without further purification.

(ii) A mixture of 5.1 g of the above-mentioned compound, 200 ml of toluene, 36 ml of cyclohexanone and 3.6 g of aluminum *iso*-propoxide was refluxed for 3 hours. After cooling to room temperature, ethyl acetate was added and the mixture was washed repeatedly with a 75 % w/v solution of Seignette salt. The organic layer was washed with water, brine, and dried over magnesium sulfate. Evaporation of the solvent under reduced pressure followed by chromatography afforded 4 g of (17β)-4',5'-dihydrospiro[estra-5(10),9(11)-diene-17,2'(3'H)-furan]-3,3'-dione 3-cyclic 1,2-ethane-diyl acetal, m.p. 146 °C.

d. To a suspension of 3.09 g of methyltriphenylphosphonium bromide in 25 ml of toluene were added 0.83 g of potassium *tert*-butoxide. The mixture was refluxed for 45 min, and then cooled, after which a solution of 1.10 g of the acetal of c(ii) in 2 ml of toluene were added and the mixture was refluxed for 1 hour. The suspension was subsequently poured into ice-water, the toluene layer separated, washed with brine, dried over magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed to afford 0.95 g of (17α)-17,23-epoxy-19,24-dinorchola-5(10),9(11),20-trien-3-one 3-

cyclic 1,2-ethanediyl acetal, m.p. 132 °C.

e.

(i) To a solution of 3.7 g of 17α)-17,23-epoxy-19,24-dinorchola-5(10),9(11),20-trien-3-one 3-cyclic 1,2-ethanediyl acetal in 25 ml of dichloromethane were added 5 g of sodium hydrogen carbonate. To this mixture was added at -40 °C a solution of 2.5 g of *meta*-chloroperbenzoic acid in 15 ml of dichloromethane. After stirring for 30 min at 0 °C, the mixture was poured into ice-water and extracted with dichloromethane. The organic layer was washed with a sodium hydrogen carbonate solution and with water, dried over magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed to give 1.8 g of the intermediate 5α,10α-epoxide.

(ii) To a solution of [4-N,N-(dimethylamino)phenyl]-magnesium bromide (prepared from 4.4 g of 4-bromo-N,N-dimethylaniline and 0.6 g of magnesium) in 40 ml of tetrahydrofuran were added 0.5 g of copper(I) chloride at room temperature. Subsequently, 1.8 g of the 5α,10α-epoxide of e(i) in 10 ml of tetrahydrofuran were added and stirring was continued for 30 min. The mixture was poured into an ammonium chloride solution and extracted with ethyl acetate. After washing with water, the organic layer was dried over magnesium sulfate and concentrated under reduced pressure. The residue was chromatographed to afford 1.4 g of the intermediate (5α,11β,17α)-17,23-epoxy-5-hydroxy-11-[(4-dimethylamino)phenyl]-19,24-dinorchola-9,20-dien-3-one 3-cyclic 1,2-ethanediyl acetal.

(iii) 1.4 g of the acetal of e(ii) in 15 ml of 70% acetic acid were heated for 2 hours at 50 °C. After cooling to room temperature the mixture was neutralized with sodium hydrogen carbonate and extracted with ethyl acetate. After drying over magnesium sulfate, the solvent was evaporated and the residue chromatographed to give 0.9 g of (11β,17α)-17,23-epoxy-11-[(4-dimethylamino)phenyl]-19,24-dinorchola-4,9,20-trien-3-one, m.p. 168 °C, $[\alpha]_D^{20}$ = +125° (c = 1.135, dioxane).

EXAMPLE 2

In an analogous manner as described in Example 1 were prepared:

(7β,11β,17α)-17,23-epoxy-7-methyl-11-[(4-dimethylamino)phenyl]-19,24-dinorchola-4,9,20-triene-3-one, m.p. 100 °C, $[\alpha]_D^{20}$ = +368° (c = 1.02, dioxane).

(11β,17α)-11-(4-acetylphenyl)-17,23-epoxy-19,24-dinorchola-4,9,20-trien-3-one, m.p. 126 °C, $[\alpha]_D^{20}$ = +82° (c = 0.955, dioxane).

(11β,17α)-11-(4-methoxyphenyl)-17,23-epoxy-19,24-dinorchola-4,9,20-trien-3-one, m.p. 185 °C.

(6β,11β,17α)-17,23-epoxy-6-methyl-11-(4-dimethylaminophenyl)-19,24-dinorchola-4,9,20-trien-3-one, m.p. 89 °C, $[\alpha]_D^{20}$ = +128° (c = 1.03, dioxane).

(11β,17α)-17,23-epoxy-11-(4-methylthiophenyl)-19,24-dinorchola-4,9,20-trien-3-one. m.p. 186 °C; $[\alpha]_D^{20}$ = +121° (c = 1.155, dioxane).

The E and Z-ethylidene derivatives were prepared analogously to the preparation of (11β,17α)-11-[(4-dimethylamino)phenyl]-17,23-epoxy-19,24-dinorchola-4,9,20-trien-3-oneby using ethyl triphenylphosphonium bromide. Separation by chromatography afforded: (3'E,11β,17β)-11-[(4-dimethylamino)phenyl]-3'-ethylidene-4',5'-dihydrospiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one. m.p. 175 ° C; $[\alpha]_D^{20}$ = +128° (c = 0.885, dioxane).

(3'Z,11β,17β)-11-[(4-dimethylamino)phenyl]-3'-ethyl-idene-4',5'-dihydrospiro[estra-4,9-diene-17,2'(3'H)-furan]-3-one. m.p. 172 °C.

EXAMPLE 3

The intermediate of Example 1d can also be prepared by treatment of (17β)-4',5'-dihydrospiro[estra-5-(10),9(11)-diene-17,2'(3'H)-furan]-3,3'-dione 3-cyclic 1,2-ethanediyl acetal with trimethylsilylmethylmagnesium chloride, followed by acid treatment.

EXAMPLE 4

The intermediate of Example 1c(ii) can also be prepared by converting the known estra-5(10),9(11)-dien-3,17-dione 3-cyclic 1,2-ethanediyl acetal (A. Belanger, D. Philibert, and G. Teutsch, Steroids, 37 - (1981), 361-383) in a similar manner as described by D. Gange and Ph. Magnus, J. Am. Chem. Soc., 100 - (1978), 7747-7748:

(i) To 65 ml of n-butyllithium (1.6 M solution in hexane) in 48 ml of tetrahydrofuran were added 9.3 ml of 1-methoxy-1,2-propadiene at -78 °C. After stirring for 45 min at this temperature 10.6 g of estra-5(10),9-(11)-diene-3,17-dione 3-cyclic 1,2-ethanediyl acetal were added. Subsequently, the mixture was stirred at

-40 °C for 30 min and poured into an ice-cold ammonium chloride solution. Ethyl acetate was added and the layers were separated. The organic layer was washed with brine, dried over magnesium sulfate and the solvent was removed under reduced pressure.

(ii) The crude 1,2-propadiene was mixed with 230 ml of *tert*-butanol, 3.75 g of potassium *tert*-butoxide and 0.3 g of dicyclohexano-18-crown-6. After refluxing for 8 hours, the mixture was poured into water and extracted with ethyl acetate. The organic layer was dried over magnesium sulfate, evaporated, and the residue was chromatographed to afford 9.1 g of the methyl enol ether of (17β)-4',5'-dihydrospiro[estra-5-(10),9(11)-diene-17,2'(3'H)-furan]-3,3'-dione 3-cyclic 1,2-ethanediyl acetal.

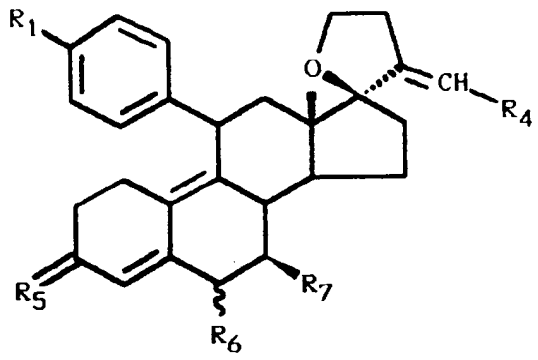
(iii) This enol ether was dissolved in 70 ml of acetone and a 1 M hydrochloric acid solution was added until pH 2. The mixture was stirred for 3 h, subsequently poured into a sodium hydrogen carbonate solution, and extracted with ethyl acetate. After drying over magnesium sulfate and removal of the solvent, the residue was subjected to chromatography to yield 6.4 g of (17β)-4',5'dihydro-spiro[estra-5-(10),9(11)-diene-17,2'(3'H)-furan]-3,3'-dione 3-cyclic 1,2-ethanediyl acetal.

EXAMPLE 5

The intermediate of Example 1d can also be prepared in one step by reaction of estra-5(10),9(11)-dien-3,17-dione 3-cyclic 1,2-ethanediyl acetal with 4-chloro-2-lithio-1-butene. Finally introduction of the 20-21 double bond into the cholane system could also be effected by an elimination reaction of an (17α,20xi)-17,23-epoxy-24-norcholane precursor possessing a suitable leaving group in either the 20- or the 21-position.

Claims

1. A 17-spirofuran-3'-ylidene steroid having the formula



I

R_1 is NR_2R_3, C(2-6) acyl, O-C(1-6) alkyl or S-C(1-6) alkyl;
R_2 and R_3 are independently selected from hydrogen and C(1-6) alkyl;
R_4 is hydrogen or C(1-6) alkyl;
R_5 is O, (H,H);
R_6 and R_7 are both hydrogen, or one is hydrogen and the other C(1-6) alkyl; and
the twitched line represents an α or β bond.

2. The 17-spirofuran-3'-ylidene steroid of claim 1, wherein
R_1 is $N(CH_3)_2$, acetyl, or S-(C1-6) alkyl;
R_4 is hydrogen or methyl;
R_5 is O;
R_6 and R_7 are both hydrogen, or one is hydrogen and the other methyl.

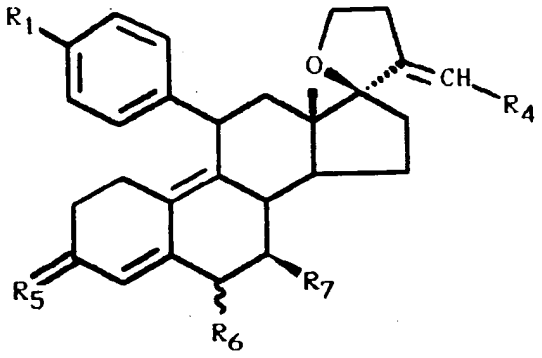
3. The 17-spirofuran-3'-ylidene steroid of claim 2, wherein R_1 acetyl, R_4 is hydrogen, R_5 is O, R_6 and R_7 are both hydrogen.

4. The 17-spirofuran-3'-ylidene steroid of any one of claims 1-3, for use in therapy.

5. A pharmaceutical composition comprising the 17-spirofuran-3'-ylidene steroid of any one of claims 1-3 and pharmaceutically acceptable auxiliaries.

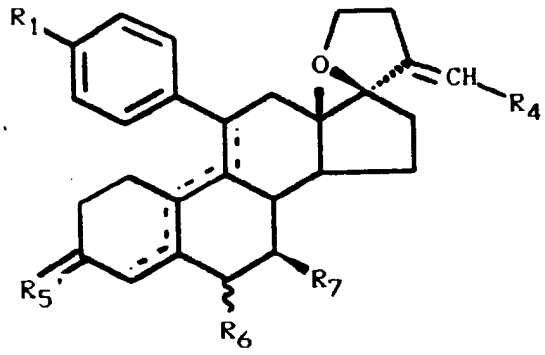
6. A use of the the 17-spirofuran-3'-ylidene steroid of any one of claims 1-3 for the manufacture of a medicament having antiprogestin activity.

7. Method of synthesis of a 17-spirofuran-3'-ylidene steroid having the formula



I

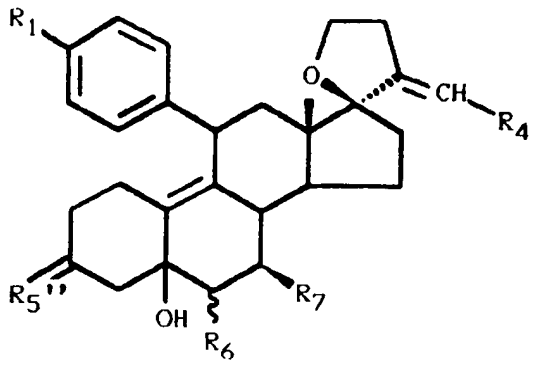
R_1 is NR_2R_3, C(2-6) acyl, O-C(1-6) alkyl or S-C(1-6) alkyl;
R_2 and R_3 are independently selected from hydrogen and C(1-6) alkyl;
R_4 is hydrogen or C(1-6) alkyl;
R_5 is O, (H,H);
R_6 and R_7 are both hydrogen, or one is hydrogen and the other C(1-6) alkyl; and
the twitched line represents an α or β bond;
characterized in that
a) a 3-keto or 3-oxim protective group in a compound having the formula



II

wherein
R_1 is NR_2R_3, C(2-6) acyl, O-C(1-6) alkyl, or S-C(1-6) alkyl;
R_2 and R_3 are independently selected from hydrogen and C(1-6) alkyl;
R_4 is hydrogen or C(1-6) alkyl;
R_5' is a protected O;
R_6 and R_7 are both hydrogen, or one is hydrogen and the other C(1-6) alkyl; the dotted line represents two conjugated bonds, and
the twitched line represents an α or β bond, is removed; or

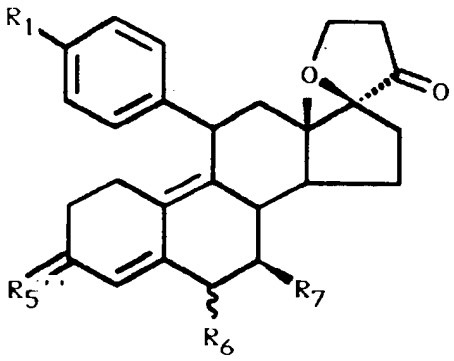
b) a compound having formula



III

wherein
R_5'' is protected O, or (H,H), and R_1-R_4, R_6-R_7, and the twitched line have the previously given meanings, is dehydrated and simultaneously cleaved or followed by cleavage of an optionally present protective group; or

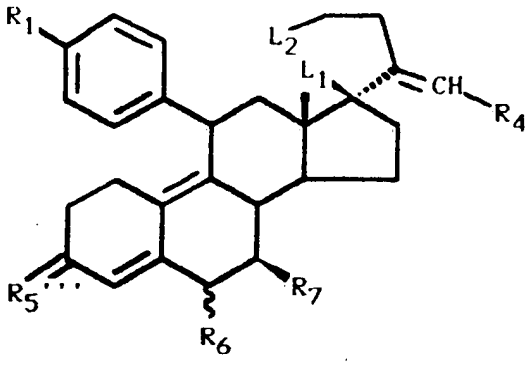
c) a compound having the formula



IV

wherein R_5'' is protected O, (H,H), and R_1-R_3, R_6-R_7, and the twitched line have the previously given meanings, is condensed with an R_4-CH_2-Wittig, R_4-CH_2-Wittig-like, or R_4-CH_2-Peterson reagent, wherein R_4 has the previously given meaning, followed by deprotection of an optionally present protective group into the 17-spirofuran-3'-ylidene steroid of formula I; or

d) a compound having the formula



V

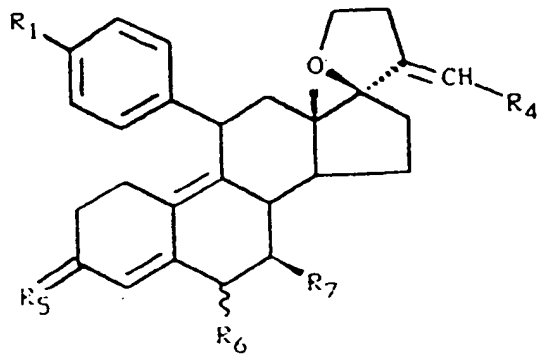
wherein R_5''' is R_5 or protected O, or (H,H),
and R_1-R_7, and the twitched line have the previously given meanings, and one of L_1 and L_2 is OH and the other is a leaving group, is converted into a 17-spirofuran-3'-ylidene steroid, which after deprotection of an optionally present protective group affords the 17-spirofuran-3'-ylidene steroid of formula I.

8. Process according to claim 7, wherein
R_1 is $N(CH_3)_2$, acetyl, or S-C(1-6) alkyl;
R_4 is hydrogen or methyl;
R_5 is O;
R_6 and R_7 are both hydrogen, or one is hydrogen and the other methyl.

9. Process according to claim 8,
wherein R_1 acetyl, R_4 is hydrogen, R_5 is O, R_6 and R_7 are both hydrogen.

Patentansprüche

1. 17-Spirofuran-3'-ylidensteroid mit der Formel:



I

worin:
R_1 NR_2R_3, C(2-6)-Acyl, 0-C(1-6)-Alkyl oder S-C(1-6)-Alkyl ist;
R_2 und R_3 unabhängig aus Wasserstoff und C(1-6)-Alkyl ausgewählt werden;
R_4 Wasserstoff oder C(1-6)Alkyl ist;
R_5 O oder (H, H) ist;
R_6 und R_7 beides Wasserstoff sind, oder eines Wasserstoff ist und das andere C(1-6)-Alkyl; und die gewellte Linie eine α- oder β-Bindung darstellt.

2. 17-Spirofuran-3'-ylidensteroid nach Anspruch 1, worin:
R_1 $N(CH_3)_2$, Acetyl oder S-C(1-6)-Alkyl ist;
R_4 Wasserstoff oder Methyl ist;
R_5 O ist;
R_6 und R_7 beides Wasserstoff sind, oder eines Wasserstoff ist und das andere Methyl.

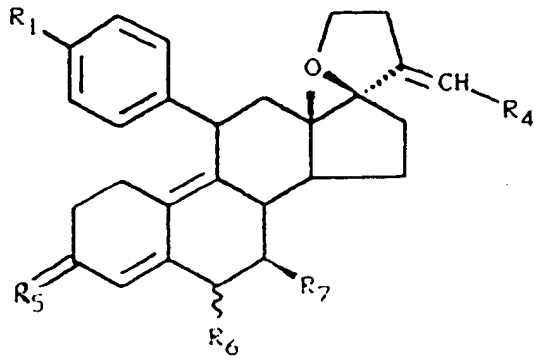
3. 17-Spirofuran-3'-ylidensteroid nach Anspruch 2, worin R_1 Acetyl, R_4 Wasserstoff, R_5 O ist und R_6 und R_7 beides Wasserstoff sind.

4. 17-Spirofuran-3'-ylidensteroid nach einem der Ansprüche 1 bis 3 zur Verwendung in einer Therapie.

5. Pharmazeutische Zusammensetzung umfassend das 17-Spirofuran-3'-ylidensteroid nach einem der Ansprüche 1-3 und pharmazeutisch annehmbare Hilfsmittel.

6. Verwendung des 17-Spirofuran-3'-ylidensteroids nach einem der Ansprüche 1 bis 3 zur Herstellung eines Medikaments, das Antiprogestinaktivität aufweist.

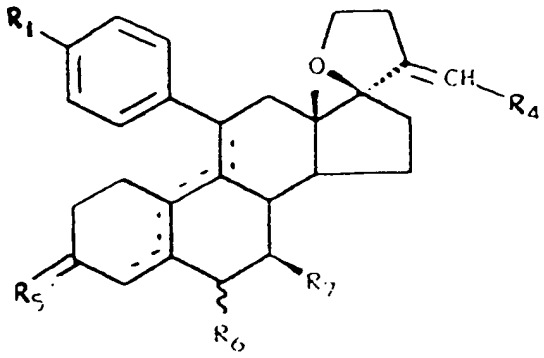
7. Verfahren zur Synthese eines 17-Spirofuran-3-'ylidensteroids mit der Formel:



I

worin:
R_1 NR_2R_3, C(2-6)-Acyl, O-C(1-6)-Alkyl oder S-C(1-6)-Alkyl ist;
R_2 und R_3 unabhängig aus Wasserstoff und C(1-6)-Alkyl ausgewählt werden;
R_4 Wasserstoff oder C(1-6)-Alkyl ist;
R_5 O oder (H,H);
R_6 und R_7 beides Wasserstoff sind, oder eines Wasserstoff ist und das andere C(1-6)-Alkyl; und die gewellte Linie eine α- oder β-Bindung darstellt;
dadurch gekennzeichnet, dass

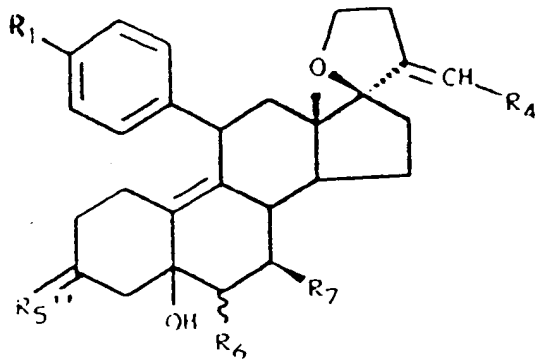
a) eine 3-Keto- oder 3-Oxim-Schutzgruppe in einer Verbindung mit der Formel:



II

worin:
R_1 NR_2R_3, C(2-6)-Acyl, O(1-6)-Alkyl oder S-C(1-6)-Alkyl ist;
R_2 und R_3 unabhängig aus Wasserstoff und C(1-6)-Alkyl ausgewählt werden;
R_4 Wasserstoff oder C(1-6)-Alkyl ist;
R_5' ein geschütztes O ist;
R_6 und R_7 beides Wasserstoff sind, oder eines Wasserstoff ist und das andere (C(1-6)-Alkyl;
die punktierte Linie zwei konjugierte Bindungen darstellt; und die gewellte Linie eine α- oder β-Bindung darstellt, entfernt wird; oder

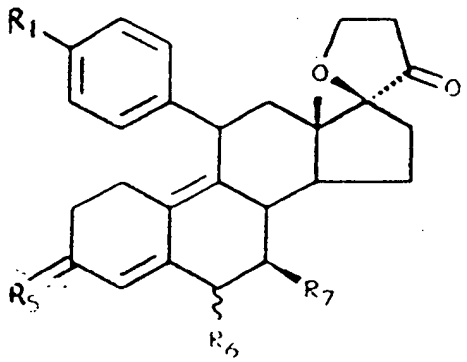
b) eine Verbindung mit der Formel:



III

worin:
R_5'' geschütztes O oder (H,H) ist und R_1-R_4, R_6-R_7 und die gewellte Linie die vorgängig erwähnten Bedeutungen haben, dehydriert wird und gleichzeitig gespalten oder von der Spaltung einer wahlweise vorhandenen Schutzgruppe gefolgt wird; oder

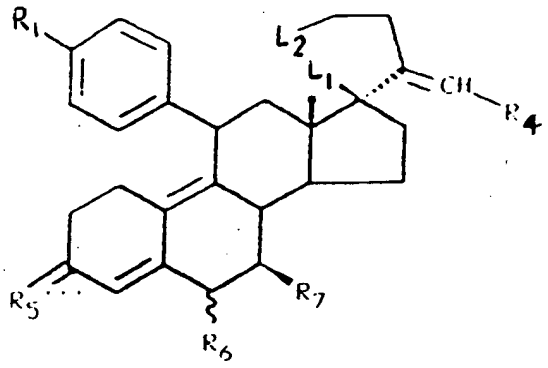
c) eine Verbindung mit der Formel:



IV

worin:
R_5'' geschütztes O oder (H,H) ist und R_1-R_3, R_6-R_7 und die gewellte Linie die vorgängig erwähnten Bedeutungen haben, mit einem R_4-CH_2-Wittig-, R_4-CH_2-Wittig-ähnlichem oder R_4-CH_2-Peterson-Reagens kondensiert wird, worin R_4 die vorgängig erwähnte Bedeutung hat, gefolgt vom Entfernen einer gegebenenfalls vorhandenen Schutzgruppe in das 17-Spirofuran-3'-ylidensteroid der Formel I; oder

d) eine Verbindung mit der Formel



V

worin:
R_5''' R_5 oder geschütztes O oder (H,H) ist und R_1-R_7 und die gewellte Linie die vorgängig

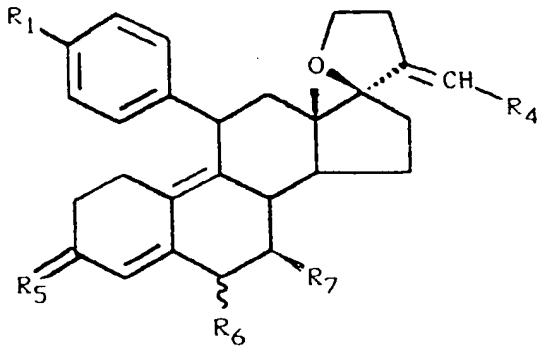
erwähnten Bedeutungen haben, und entweder L_1 oder L_2 OH ist und das andere eine austretende Gruppe, in ein 17-Spirofuran-3'-ylidensteroid umgewandelt wird, das nach dem Entfernen einer gegebenenfalls vorhandenen Schutzgruppe das 17-Spirofuran-3'-ylidensteroid der Formel I liefert.

8. Verfahren nach Anspruch 7, worin:
R_1 $N(CH_3)_2$, Acetyl oder S-C(1-6)-Alkyl ist;
R_4 Wasserstoff oder Methyl ist;
R_5 O ist;
R_6 und R_7 beides Wasserstoff sind, oder eines Wasserstoff und das andere Methyl ist.

9. Verfahren nach Anspruch 8, worin
R_1 Acetyl, R_4 Wasserstoff, R_5 O ist und R_6 und R_7 beides Wasserstoff sind.

Revendications

1. Un 17-spirofuranne-3'-ylidène stéroïde répondant à la formule



I

dans laquelle
R_1 représente NR_2R_3, un radical acyle en C_2 à C_6, un radical O-alkyle en C_1 à C_6 ou un radical S-alkyle en C_1 à C_6;
R_2 et R_3 sont indépendamment sélectionnés parmi un atome d'hydrogène et un radical alkyle en C_1 à C_6,;
R_4 représente un atome d'hydrogène ou un radical alkyle en C_1 à C_6;
R_5 représente O, (H,H);
R_6 et R_7 représentent tous deux un atome d'hydrogène ou l'un d'entre eux représente un atome d'hydrogène et l'autre un radical alkyle en C_1 à C_6; et
le trait sinueux représente une liaison α ou β.

2. Le 17-spirofuranne-3'-ylidène stéroïde selon la revendication 1, dans lequel
R_1 représente $N(CH_3)_2$, un radical acétyle ou S-alkyle en C_1 à C_6;
R_4 représente un atome d'hydrogène ou un radical méthyle;
R_5 représente O;
R_6 et R_7 sont tous deux un atome d'hydrogène, ou l'un représente un atome d'hydrogène et l'autre un radical méthyle.

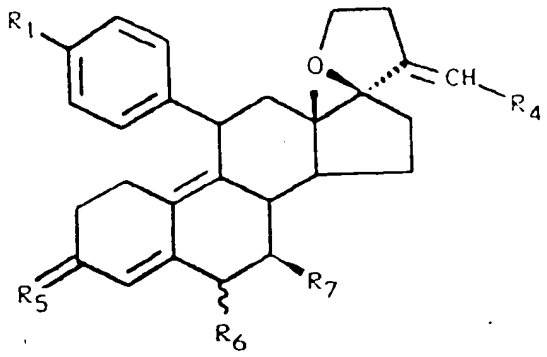
3. Le 17-spirofuranne-3'-ylidène stéroïde selon la revendication 2, dans lequel R_1 représente un radical acétyle, R_4 représente un atome d'hydrogène, R_5 représente O, et R_6 et R_7 sont tous deux un atome d'hydrogène.

4. Le 17-spirofuranne-3'-ylidène stéroïde selon l'une quelconque des revendications 1 à 3, pour une utilisation en thérapie.

5. Une composition pharmaceutique comprenant le 17-spirofuranne-3'-ylidène stéroïde selon l'une quelconque des revendications 1 à 3 et des additifs pharmaceutiquement acceptables.

6. L'utilisation du 17-spirofuranne-3'-ylidène stéroïde selon l'une quelconque des revendications 1 à 3 pour la préparation d'un médicament présentant une activité antiprogestative.

7. Procédé de synthèse d'un 17-spirofuranne-3'-ylidène stéroïde répondant à la formule



I

R_1 représente NR_2R_3, un radical acyle en C_2 à C_6, un radical O-alkyle en C_1 à C_6 ou un radical S-alkyle en C_1 à C_6;

R_2 et R_3 sont indépendamment sélectionnés parmi un atome d'hydrogène et un radical alkyle en C_1 à C_6,;

R_4 représente un atome d'hydrogène ou un radical alkyle en C_1 à C_6;

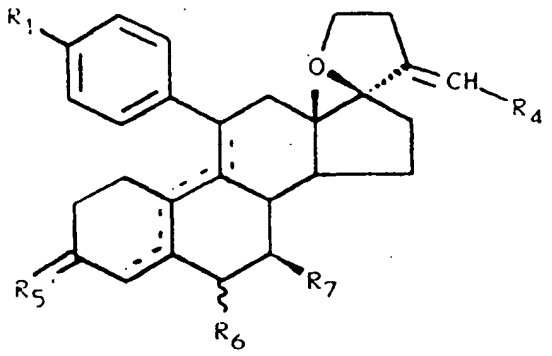
R_5 représente O, (H,H);

R_6 et R_7 représentent tous deux un atome d'hydrogène ou l'un d'entre eux représente un atome d'hydrogène et l'autre un radical alkyle en C_1 à C_6; et

le trait sinueux représente une liaison α ou β;

caractérisé en ce que:

a) un groupe protecteur 3-céto ou 3-oxime dans un composé répondant à la formule



II

dans laquelle

R_1 représente NR_2R_3, un radical acyle en C_2 à C_6, un radical O-alkyle en C_1 à C_6 ou un radical S-alkyle en C_1 à C_6;

R_2 et R_3 sont indépendamment sélectionnés parmi un atome d'hydrogène et un radical alkyle en C_1 à C_6,;

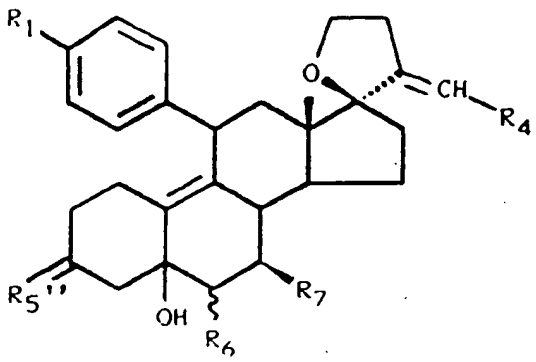
R_4 représente un atome d'hydrogène ou un radical alkyle en C_1 à C_6;

R_5' représente un O protégé;

R_6 et R_7 représentent tous deux un atome d'hydrogène ou l'un représente un atome d'hydrogène et l'autre un radical alkyle en C_1 à C_6; la ligne en pointillé représente deux liaisons conjuguées; et

le trait sinueux représente une liaison α ou β, est éliminé; ou bien

b) un composé répondant à la formule

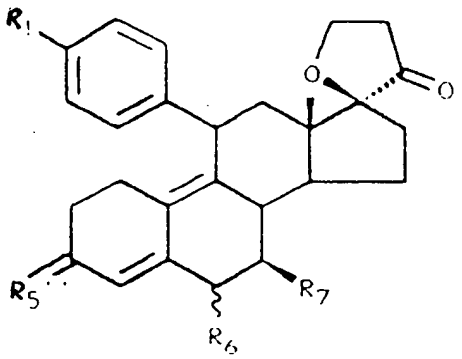


III

dans laquelle

$R_{5''}$ est un O protégé ou (H,H), et R_1-R_4, R_6-R_7 ainsi que le trait sinueux ont la signification donnée ci-dessus, est déshydraté et simultanément ou successivement soumis ensuite à un clivage d'un groupe protecteur éventuellement présent; ou

c) un composé répondant à la formule

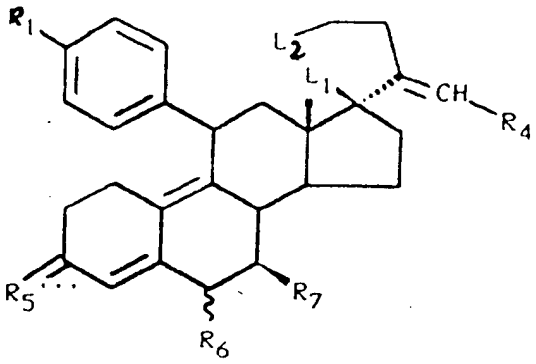


IV

dans laquelle $R_{5''}$ correspond à un O protégé, (H,H), et R_1-R_3, R_6-R_7 ainsi que le trait sinueux la signification donnée ci-dessus, est condensé avec un réactif R_4-CH_2-Wittig, R_4-CH_2-type Wittig ou R_4-CH_2-Peterson,

dans lesquels R_4 a la signification donnée ci-dessus, puis soumis à une étape d'élimination d'un groupe protecteur éventuellement présent pour donner le 17-spirofuranne-3'-ylidène stéroïde de formule I, ou bien,

d) un composé répondant à la formule



V

dans laquelle $R_{5'''}$ représente un groupe R_5 ou un O protégé, ou (H,H), et R_1-R_7 ainsi que le trait sinueux ont la signification donnée ci-dessus, et un des groupes L_1 et L_2 représente un groupe OH

et l'autre un groupe partant, est converti en un 17-spirofuranne-3'-ylidène stéroïde, puis est soumis à une élimination d'un groupe protecteur éventuellement présent pour donner le 17-spirofuranne-3'-ylidène stéroïde de formule I.

8. Procédé selon la revendication 7, dans lequel
R_1 représente $N(CH_3)_2$, un radical acétyle ou S-alkyle en C_1 à C_6;
R_4 représente un atome d'hydrogène ou un radical méthyle;
R_5 représente O;
R_6 et R_7 sont tous deux un atome d'hydrogène, ou l'un représente un atome d'hydrogène et l'autre un radical méthyle.

9. Procédé selon la revendication 8, dans lequel R_1 représente un radical acétyle, R_4 est un atome d'hydrogène, R_5 représente O, R_6 et R_7 sont tous les deux un atome d'hydrogène.